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Invited review

The role of dopaminergic midbrain in Alzheimer's disease: Translating basic science into clinical practice

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ABSTRACT

Mammalian brain cortical functions, from executive and motor functioning to memory and emotional regulation, are strictly regulated by subcortical projections. These projections terminate in cortical areas that are continuously influenced by released neurotransmitters and neuromodulators.

Among the subcortical structures, the dopaminergic midbrain plays a pivotal role in tuning cortical functions that commonly result altered in many neurological and psychiatric disorders. Incidentally, extensive neuropathological observations support a strong link between structural alterations of the dopaminergic midbrain and significant behavioural symptomatology observed in patients suffering from Alzheimer 's disease(AD).

Here, we will review recent progress on the involvement of the dopaminergic system in the pathophysiology of AD as well as the current therapeutic strategies targeting this system.

Contents

1. Introduction

Alzheimer's disease (AD), including the genetically inherited form for which exist a family medical history [1,2] is a progressive neurological disorder causing dementia in an increasingly large proportion of the aging worldwide population. Its main hystopathological hallmarks are extracellular accumulation of neuritic plaques of β-amyloid (Aβ) peptide, and intracellular deposition of protein tau aggregates even though there is evidence of synaptic dysfunctions preceding these macroscopic features [3,4]. Indeed, studies on the Tg2576-APPswe (Tg2576) mouse model of AD have shown early enhancement of hippocampal long-term depression (LTD) [5,6] and reduced long-term potentiation (LTP) [7], before Aβ plaques appearance. Furthermore, subcortical dysfunctions have been reported in AD patients, including reduced levels of dopamine (DA), causing psychiatric symptoms like apathy and depression, and possibly taking part in cognitive decline [8–11]. This observation is particularly intriguing in view of the functional crosstalk between the mesolimbic network and the hippocampus whereby the latter provides a major excitatory input to the nucleus

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accumbens (NAcc) [12], finally favouring Ventral Tegmental Area (VTA) DA signaling to target regions, including the hippocampus [13,14].

The present review, besides providing an overview of the dopaminergic midbrain system, will focus on the recent progress in the characterization of early phase of AD, particular attention being paid to new and promising findings, which could be useful in early diagnosis and therapy.

2. Chemo-architecture of the dopaminergic midbrain system

The mesencephalic dopaminergic (DAergic) cells, which have been largely subdivided in two groups, provide the brain with the neurotransmitter DA. In fact, it is known that the ventral tegmental area (VTA, A10) DAergic neurons mainly project to the NAcc, amygdala and the cerebral cortex, while the substantia nigra pars compacta neurons (SNpc, A9) mainly project to the dorsal striatum. This anatomical separation is somehow related to the various functions of the DAergic system, being the VTA neuronal activity mainly linked to reward, working memory and vigilance, while the SNpc neuronal activity principally linked to voluntary motor activity. Although this anatomical and functional subdivision is questioned, it is certain that there are different genetic and molecular markers in these cells.

The spontaneously firing DAergic cells in the VTA and SNpc have typical but also varying electrophysiological and pharmacological characteristics that are related to their location in the mesencephalon. For instance there is latero-medial gradient (from the lateral SNpc to the medial VTA) for the reduction of input resistance, inward rectifying hyperpolarizing current (Ih) and autoreceptor-mediated inhibition, whereas the connections of the DAergic cells somehow differ in the VTA and the SNpc [15].

The VTA neurons that project to the cortex constitute the meso-cortical pathway; those projecting to the NAcc and hippocampus constitute the mesolimbic pathway, while projections to the basolateral amygdala constitute the meso-amygdaloid DAergic pathway. These cells receive excitatory inputs from the cortex and the pedunculo-pontine nucleus while the main inhibitory inputs arise from the NAcc and from local interneurons [16].

This scheme is replicated for SNpc neurons, which mainly project to the striatum, constituting the nigro-striatal pathway. The SNpc DAergic cells receive excitatory inputs from the cortex, the subthalamic and pedunculo-pontine nuclei, whereas the striato-nigral direct pathway and the local interneurons provide the SNpc cells with inhibitory inputs [17].

Apart from the different sensitivity of DAergic neurons to DA (with the medial VTA neurons being less sensitive to dopamine D2 receptor-mediated inhibition via activation of G protein-coupled inwardly-rectifying potassium channels) [18], the DAergic cells respond to other neurotransmitters/neuromodulators with changes in excitability. The excitatory input is mainly sustained by glutamate/aspartate acting on ionotropic (AMPA/kainate, NMDA receptors) and metabotropic (Group I, II, III) glutamate receptors [19,20]. Glutamate also acting on metabotropic receptors reduces the release of excitatory and inhibitory transmitters on DAergic neurons [21]. On the other hand, the inhibitory input is principally sustained by GABA, activating GABA-A ionotropic and GABA-B metabotropic receptors, although a glycinergic component is also present in the inhibitory responses, mediated by strychnine-sensitive receptors [22]. Of note, local DA also activates presynaptic D1 receptors located on striato-nigral terminals, to increase the release of GABA in the SNpc [23].

An opposite action (decrease of the release of GABA) is exerted by adenosine acting on presynaptic A1 receptors [24]. Additionally, noradrenaline excites the DAergic cells by activating alpha1 receptors [25].

Importantly, acetylcholine displays a plethora of actions on the DAergic neurons; the activation of nicotinic receptors excites VTA and SNpc cells [26,27] while the effects of activation of muscarinic receptors are variable. Indeed, postsynaptic M1 receptors excite the DAergic cells via a Gq-mediated mechanisms [28], whereas activation of M2/M3 receptors located presynaptically reduces neurotransmitter release [29,30], thus influencing DAergic neuronal functions. Moreover, the Group I metabotropic glutamate receptors, the M1 muscarinic receptors and the alpha-1 noradrenergic receptors, beside exciting the neurons via Gq-mediated actions, also induce the release of intracellular calcium that in turn, mediates the opening of calcium-dependent potassium channels to inhibit the cells [31–34]. The complexity of the functioning of the DAergic neurons is also dependent on the activity of various neurotransmitters/receptors that are in some cases differently distributed in the ventral mesencephalon. For instance, the alpha1 noradrenergic receptors are mainly present on VTA DAergic cells. Similar excitatory effects are also mediated by neurotensin (NTs1) [35]. An important role in controlling DAergic neuron excitability is also played by serotonin that, by activating 5HT1 B receptors, reduces both the synaptic release of GABA, which acts on GABA-B receptors [36], and glutamate that activates a mGluR1-mediated IPSC on the DAergic cells [37]. A complex interplay on the synaptic activity is also played by opioids and endocannabinoids. Endocannabinoids increase presynaptic glutamate release by activating capsaicin-sensitive vanniloid receptors [38], or reduce the release of glutamate and GABA via CB1 receptors [39,40], whereas opioids disinhibit dopaminergic neurons by a direct inhibitory effect on midbrain GABAergic interneurons [41].

These interactions could also be important to determine long-term changes in synaptic plasticity, mainly described in the VTA as consequence/cause of normal or pathological incentive behaviour [42].

There is also evidence that the DAergic cells besides releasing DA also release glutamate and GABA in their terminal areas and this could have an important impact in the physiopathological manifestations of diseases if the DAergic system is not properly functioning [43].

In conclusion, it appears that in spite of an apparent uniform picture, there are typical and distinct physiological and pharmacological features of the DAergic cells in the VTA and SNpc that might account for their different vulnerability in pathological conditions such as AD and Parkinson's disease.

3. Deficits of the dopaminergic system in AD

Several observations emerging from the study of both post-mortem AD brains and mouse models of AD suggest an involvement of theDAergic system in the pathophysiology of AD [8,9,44–46].

The first evidence dates back to the detection of mild degenerative histological abnormalities (including neurofibrillary tangles) in the SNpc and VTA in several cases of AD [45]. A few years later, it was reported [8] that the levels of DA and DA metabolites measured by high-pressure liquid chromatography in several brain regions from post-mortem AD brain were significantly reduced.

Polymorphisms associated with the DAergic transmission are associated with AD, characterised by higher neurodegeneration within DA-innervated brain structures, as reported for the polymorphism $Val^{158}Met$ in the gene encoding for cathechol-O-methyltransferase (COMT) [47]. The Met substitution leads to a lower activity of the COMT enzyme; conversely, the higher activity of COMT, caused by the Val variant, results in reduced DA levels in synaptic compartments, as a result of increased DA catabolism.

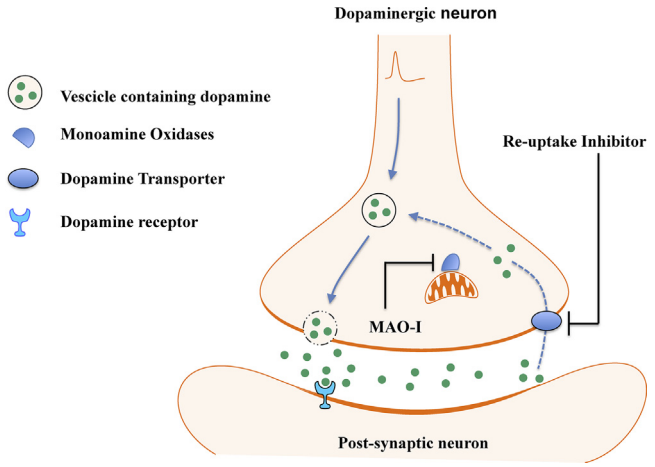

Fig. 1. The mechanism of action of both Monoamine Oxidase B and Dopamine re-uptake inhibitors.
Dopamine is released by dopamine neurons and then binds to a receptor on a neighboring cell. After this, the dopamine detaches and it is reabsorbed by the dopamine neuron via dopamine transporter.
Monoamine oxidase B (MAOB) is an enzyme involved in the metabolism of dopamine. It converts dopamine to its corresponding carboxylic acid via an aldehyde intermediate. MAOB regulates both the free intraneuronal concentration of dopamine and the releasable stores. MAOB inhibitors, such as selegiline, bind to and inhibit MAOB, preventing dopamine degradation. This results in greater stores of dopamine available for release. Similarly, by blocking dopamine transporter, more dopamine is available in synaptic cleft to stimulate post-synaptic neuron.

Overall, the reduced levels of DA characterize AD pathophysiology. Beyond this notion, the DA receptor expression has also been investigated and several authors found a reduced expression of D2 receptors in caudate, putamen, hippocampus and frontal cortex [48,49].

Experimental studies coming from mouse models of AD have confirmed the role of DA in AD, as demonstrated by the strong correlation between amyloid deposition and progressive degeneration of the dopaminergic system.

Importantly, several works demonstrated that the pharmacologically recovery the DAergic tone – with the administration of the DA precursor L-DOPA, with drugs aiming to reduce DA degradation, like monoamine oxidase-B (MAO-B) inhibitors, or with DA re-uptake inhibitors (Fig. 1) – was able to ameliorate memory and learning functions both in AD patients and in experimental animal models [50–60].

In line with this observation, a recent experimental work [61,62] on a mouse model of early AD demonstrated an age-dependent DAergic neuronal loss in the VTA in complete absence of accumulation of amyloid plaques or neurofibrillary tangles. VTA degeneration was paralleled by progressive reduction of basal DA outflow in projecting areas, including the NAcc and hippocampus, causing alterations in reward processing and memory disturbances, respectively.

Moreover, as cholinergic projections are critical for modulating the function of DAergic neurons in VTA (see previous section) we can assume that a DAergic dysfunction might be caused also by a progressive loss of cholinergic neurons in strict compliance with the cholinergic hypothesis, showing that dysfunctions of the cholinergic system in the basal forebrain account for the memory deficits observed in typical AD [63,64].

4. Neuropsychiatric symptoms in AD: a possible involvement of the dopaminergic system

The progression of AD includes functional and behavioural deficits in addition to cognitive decline. Neuropsychiatric symptoms (NPS) are hallmarks of AD and are among the earliest deficits in AD, present prior to the manifestation of dementia [65,66]. The presence of several NPS might help to predict the incidence of mild cognitive impairment, and they often reveal more powerfully than hippocampal atrophy, a recognized early marker of AD [67].

A recent longitudinal study revealed [68] that NPS are associated with eventual progression to dementia and emerge in three different phases: a) irritability, depression, and night-time behaviour changes; b) appetite changes, agitation and apathy; c) motor disturbances, hallucinations, and disinhibition.

Little is known about the neurobiology of these symptoms and, overall, about the relationship between NPS and cognitive deficits. Several studies reported the involvement of components of the limbic system, including the amygdala, basal forebrain, hypothalamus and brainstem. Despite the absence of data on the correlation between the degeneration of one or more limbic system components and both onset and progression of NPS, the noradrenergic and DAergic systems are the best candidates for a role in early AD [9,46].

There are histological e functional proofs supporting for different cerebral projections of noradrenergic and DAergic systems [69], with important etiology and treatment implication for mental disorders [70]. DA and Noradrenaline signalling may be involved in functionally opposing processes. For instance, aversive stimuli activated noradrenaline but inhibited DA signaling, whereas hedonic stimuli activated dopamine release while the release of noradrenaline was inhibited [71]. On the other hand, the noradrenaline and DA systems interact functionally. Several studies, here reported, have provided evidence supporting Locus Coeruleus (LC) regulation of DA processes.

This is demonstrated by the evidence that dopamine derives also from noradrenergic terminal, at least in cerebral cortex.

Extracellular DA in the cerebral cortex originates not only from DA but also from noradrenaline terminals [see [72], and synaptic DA is captured efficiently by both noradrenaline and DA transporters [73]. DA binds to alpha-2 adrenergic receptors albeit with lower affinity [74]. Chemical modulation or electrical stimulation of the LC alters both norepinephrine and DA concentration in the cerebral cortex, and noradrenaline fibers may be the primary source of a DA-mediated increase in synaptic transmission in the hippocampus [75]. LC may contribute to DA transmission under physiological conditions and in response to antidepressants and drugs of abuse. Taken together, these studies suggest neurobiological bases for both shared and distinct roles of the noradrenaline and DA systems in a wide range of cerebral processes, and many "complex behaviours" described in AD patients may be associated with functional alterations of these two catecholamine systems.

The LC is the major source of noradrenaline in the brain, with projections reaching the entire cerebral cortex, as well as the thalamic nuclei and hippocampus [76]. Importantly, it has been recently reported that Tyrosine Hydroxylase-positive (TH^+) neurons from LC can also co-release DA together with noradrenaline and that the majority of TH^+ projections in the hippocampus originate from LC [77]. In this case LC should be considered as the principal source of DA in the hippocampus, and is essential for hippocampal-related memory processes [78]. Both noradrenaline and DA are involved in a number of brain functions that correlate with NPS.

The DAergic functions, in particular, range from memory, motivational processes [79], to the regulation of sleep-wake regulation [80].

It is worth noting that noradrenergic transmission in the medial prefrontal cortex modulates DA transmission in the mesoaccumbens system and its control of motivated behavior in aversive or appetitive conditions [81–83].

Moreover, neuropathological observations in the brainstem of post-mortem AD brain suggest an important role for the LC in

Table 1
Dopamine-based treatments in Alzheimer's Disease.

Preclinical Trials	Clinical Trials			
	Phase I	Phase II	Phase III	Phase IV
Pazini, A.M. et al. *Neurochem. Res.* 38, 2287–2294 (2013). [54]		Rotigotine (dopamine agonist) ClinicalTrials.gov Identifier: NCT03250741	Bupropion (dopamine uptake inhibitor) ClinicalTrials.gov Identifier: NCT01047254	Levodopa (dopamine precursor) ClinicalTrials.gov Identifier: NCT00306124
Weinstock, M. et al. *Ann. N. Y. Acad. Sci.* 939, 148–161 (2001). [85]		Rasagiline ClinicalTrials.gov Identifier: NCT02359552	Risperidone (dopamine receptor antagonist) ClinicalTrials.gov Identifier: NCT00034762	Dextroamphetamine (dopamine uptake inhibitor) ClinicalTrials.gov Identifier: NCT00254033
Jürgensen, S. et al. *J. Biol. Chem.* 286, 3270–3276 (2011). [52]		Pramipexole ClinicalTrials.gov Identifier: NCT01388478		Haloperidol D_2 receptor antagonist ClinicalTrials.gov Identifier: NCT00009217
Guzmán-Ramos, K. et al. *Learn. Mem. Cold Spring Harb. N* 19, 453–460 (2012). [50]				
Tsunekawa, H., Noda, Y., Mouri, A., Yoneda, F. & Nabeshima, T. *Behav. Brain Res.* 190, 224–232 (2008). [53]				
Ambrée, O. et al. *Neurobiol. Aging* 30, 1192–1204 (2009). [58]				

AD pathophysiology. In fact, a neuroimaging study demonstrated that LC shows strong functional connectivity with the hippocampus that correlates with memory performance reduced in amnestic mild cognitive impairment patients [84]. The evidence that the LC undergoes significant functional and structural modifications in AD supports the hypothesis that reduced function of LC contributes to memory dysfunction.

Additionally to the LC dysfunctions, the latest evidence of a selective and precocious VTA DAergic cell death in a validated mouse model of AD [61], pointing to a relevance of the midbrain DAergic system in AD, has opened up new research possibilities, aiming to examine this brain area in early-phase AD patients by means of neuroimaging studies. Taken together, both preclinical results obtained from AD mouse models and clinical observations from patients underline the relevance of the DAergic system in the pathophysiology of AD.

5. Conclusions and perspectives

In recent years increasing evidence has proven a strong association between deficits in DAergic signaling and several cognitive and non-cognitive alterations related to AD.

These preclinical and clinical observations led to the assessment of therapies targeting the dopamine system (Table 1); to this end, MAO-B inhibitors as selegiline [54] and rasagiline [85] have been considered as promising therapies for AD, but unfortunately the results of such attempts are controversial, in humans [86]. Based on the recent findings obtained in an experimental model of AD [61], we can speculate that the effectiveness of selegiline could be dependent on the degree of DA neuron degeneration in the VTA, and that a MAO-B-based therapy might result effective only in an early phase of AD when the degree of midbrain degeneration is low [87].

Future neuroimaging investigations are needed to confirm the role of midbrain neurons in early AD and accelerate the development of new therapies aimed to protect the dopaminergic system.

Conflict of interest

All the authors declare no competing financial interest.

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